Dietary Phosphatidylcholine Intake and Type 2 Diabetes in Men and Women

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Recent studies have related plasma levels of gut microbiota metabolites of dietary phosphatidylcholine to risk of cardiovascular disease (1,2). Choline from dietary phosphatidylcholine can be converted by gut microbes to form trimethylamine, which is then absorbed and oxidized in the liver to form trimethyamine oxidase (3). Diet is the primary source of gut microbiota metabolites; however, little is known about the association between dietary phosphatidylcholine and risk of type 2 diabetes (T2D).

We extracted data with dietary intake from three ongoing cohorts: the Nurses' Health Study (NHS), NHS II, and the Health Professionals Follow-Up Study (HPFS). We excluded participants with diabetes ($n = 5,466$), cardiovascular disease ($n = 3,655$), cancer ($n = 8,675$), or implausible dietary data ($n = 4,009$) at baseline, leaving 203,308 men and women for analysis (NHS: 73,128; NHS II: 88,516; HPFS: 41,664). Dietary phosphatidylcholine was estimated by a valid food-frequency questionnaire (4), with approximately 130 food items administered every 2 or 4 years combined with the phosphatidylcholine contents from the U.S. Department of Agriculture database (http://www.ars.usda.gov/ba/bhnrc/ndl) and from values published by Zeisel et al. (5). Cox proportional hazards regression models were used to estimate the relative risk (RR) and 95% CI for associations between phosphatidylcholine and T2D while accounting for potential confounders, including age, BMI, lifestyle factors, family history of diabetes, and present chronic conditions (full list of covariates is available in Fig. 1).

We documented 7,063, 4,465, and 3,531 cases of T2D during the follow-ups of NHS (1984–2008), NHS II (1991–2011), and HPFS (1986–2010), respectively. Compared with people in the lowest quintiles of dietary phosphatidylcholine intakes, the multivariate-adjusted RR of T2D for those in the highest quintiles was 1.36 (95% CI 1.26–1.48) in NHS, 1.35 (95% CI 1.22–1.50) in NHS II, 1.28 (95% CI 1.14–1.44) in HPFS, and 1.34 (95% CI 1.27–1.42) in the pooled analysis. The association was 1.24 (95% CI 1.16–1.33) after further adjustment for the three major food sources (red meat, eggs, and seafoods) and 1.27 (95% CI 1.20–1.39) with all choline-containing components and betaine mutually adjusted.

With an increase of 100 mg choline from phosphatidylcholine, the risk of T2D increased by 17% (95% CI 13–22). We did not observe significant interaction between phosphatidylcholine and age, BMI, or major dietary sources of phosphatidylcholine ($P > 0.07$ for all); the association was consistent in the subgroups (Fig. 1).

Given the observational nature, our study alone could not prove causality. Similar to other observational studies, it was difficult to rule out residual confounding, even though we carefully controlled for the potential confounders in the analyses. In addition, measurement errors were inevitable in the estimates of food and nutrient intakes. Adjustment for energy intake and use of cumulatively average intake levels might reduce the magnitude of measurement errors to some extent.

In summary, for the first time our study associated dietary intakes of phosphatidylcholine with incident T2D risk in multiple prospective cohorts with a large sample size, high rates of long-term follow-up, and detailed and repeated assessments of diet and lifestyle. Our findings lend support to dietary intervention strategies targeting dietary sources of gut microbiota metabolites in prevention of T2D.

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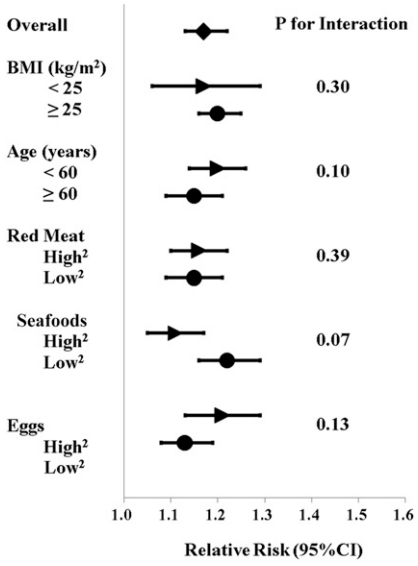

Figure 1—Stratified analysis of the association between choline from phosphatidylcholine (per 100 mg/day) and risk of T2D, adjusted for age (months), BMI (kg/m^2), menopausal status (pre- or postmenopausal [never, past, or current menopausal hormone use], women only), family history of diabetes (yes/no), smoking status (never smoker, former smoker, current smoker [1–14, 15–24, or ≥25 cigarettes/day]), alcohol drinking (0, 0.1–4.9, 5.0–14.9, 15.0–19.9, 20.0–29.9, or ≥30 g/day), moderate/vigorous-intensity activities (0, 0.01–1.0, 1.0–3.5, 3.5–6.0, or ≥6 h/week), presence of hypertension and hypercholesterolemia (each yes/no), and dietary intakes of energy, cereal fiber, *trans* fat, coffee, ratio of polyunsaturated to saturated fat, sugar-sweetened beverages, and glycemic index (quintiles). [2]Cut-off points, cohort-specific median values.

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Author Contributions. Y.L. and L.Q. conceived and designed the study. Y.L., D.D.W., S.E.C., J.E.M., W.C.W., F.B.H., and L.Q. analyzed and interpreted the data, contributed statistical expertise, performed critical revision of the article for important intellectual content, and gave final approval of the article. Y.L. drafted the manuscript. J.E.M., W.C.W., F.B.H., and L.Q. provided the study materials or patients and collected and assembled the data. Y.L. and L.Q. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013; 368:1575–1584
2. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472:57–63
3. Zeisel SH, Wishnok JS, Blusztajn JK. Formation of methylamines from ingested choline and lecithin. J Pharmacol Exp Ther 1983;225: 320–324
4. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–867
5. Zeisel SH, Mar MH, Howe JC, Holden JM. Concentrations of choline-containing compounds and betaine in common foods. J Nutr 2003;133:1302–1307